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The Association between Adolescent Marijuana Use and Early Adulthood Depression

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Abstract

Marijuana is one of the most widely used drugs in the United States, and the consequences of its use are mostly unknown. As marijuana becomes legalized and more widely available, it is important to investigate possible cognitive and mental health consequences of its use. The present study examined the associations between childhood internalizing behavior, adolescent marijuana use and early adulthood depression. A twin study was conducted to examine two alternative hypotheses regarding the association between adolescent marijuana use and early adulthood depression: 1. the association between marijuana use and depression is due to common genes or shared environmental influences, 2. after controlling for genetics and environmental factors on early internalizing behavior, the non-shared environmental factors that lead to marijuana use also lead to depression in adulthood (i.e., result more consistent with the causal hypothesis). There was a positive, statistically significant correlation between adolescent marijuana use and early adulthood depression, which was mostly explained by common shared environmental influences. There was little evidence that marijuana use has a causal influence on depression.

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Introduction

Marijuana is the most widely used federally illicit drug in the United States (Johnston, O'Malley, Miech, Bachman, & Schulenberg, 2016). A yearly survey of middle and high school students (Johnston et al., 2015) reported that rates of marijuana use have been increasing since 1992 before leveling off and holding through 2015. There has also been a recent decrease in perceived risk and disapproval of marijuana use. Currently, twenty-three states as well as the District of Columbia have legalized medical marijuana, while four states (Alaska, Colorado, Oregon and Washington) and the District of Columbia have legalized recreational marijuana (National Conference of State Legislatures, 2016). Although availability of marijuana has declined among younger adolescents, it remains widely available to older adolescents, with 80% of 12th graders reporting that marijuana is 'fairly' or 'very' easy to obtain (Johnston et al., 2015). As marijuana use becomes legalized at the state level, it is important to understand the consequences of its use. Marijuana legalization may increase availability to adolescents and lead to greater social acceptance of use, lower prices, and new formulations with higher potencies (Hopfer, 2014). To date, marijuana use has been associated with increased rates of mental illness, such as psychosis (e.g., Moore et al. 2001; Fergusson, Horwood, & Ridder, 2005) and depression (e.g. Degenhardt, Hall, & Lynskey, 2003), as well as chronic cognitive deficits (e.g., Lubman, Cheetham & Yucel, 2015). The present study addressed the association between adolescent marijuana use and early adulthood depression, and tested alternative hypotheses explaining the association.

Although there is evidence for an association between marijuana use and depression, the literature includes some inconsistent findings. Degenhardt et al. (2013) found that although there were cross-sectional associations between marijuana use and depression in some instances, there

was no indication that adolescent marijuana use is associated with major depressive episodes at age 29. Similarly, Manrique-Garcia, Zammit, Dalman, Hemmingsson, and Allebeck (2012) found that marijuana use between ages 18-20 did not increase the likelihood of developing depression that required hospitalization in the following 35 years. In contrast, Gage et al. (2015) concluded that marijuana use at 16 increased the likelihood of developing depression at age 18. Further, a literature review by Renard, Krebs, Le Pen, and Jay (2014) found evidence that early onset and regular use of marijuana increases the likelihood of developing depression later in life. Several of these articles suggest that a causal association between marijuana use and depression is a viable hypothesis (Renard et al., 2014; Degenhardt, Hall, & Lynskey, 2003). Suggested mechanisms for causal influence include the possibility that THC affects serotonin and other neurotransmitters, producing depressive symptoms, or that heavy marijuana use may lead to depression by affecting psychological adjustment (Degenhardt et al., 2003).

Although it is possible that marijuana use has a causal influence on later depression, alternative hypotheses must be considered. Notably, an association between the variables of interest may be due to confounding factors that influence both the independent and the dependent variable. For example, if childhood behavior problems are risk factors for both later marijuana use and depression, the childhood behavior problem is a confounding variable. Degenhardt et al. (2003) noted that common genetic or environmental factors influencing both marijuana use and depression may be an explanation for this association.

Several studies have tried to adjust for confounding variables by using statistical control. Manrique-Garcia, et al. (2012) found that there is an association between using large quantities of marijuana and meeting criteria for severe depression, but the association was no longer significant after statistically controlling for a number of confounders. The authors concluded that

disturbed behavior in childhood (defined as school absences, contact with police and childcare authorities, running away from home, and school sanctions) was the variable that explained the most covariance between marijuana use from 18 to 20 and increased depressive symptoms later in life. Green and Ritter (2000) conducted a cross-sectional study and found that the effect of early marijuana use on later depression is explained by decreased levels of educational attainment, employment and marriage status, as well as the frequency of alcohol and tobacco use. Harder et al. (2006) found that although there was an initial association between ongoing marijuana use and depression, the association was reduced significantly once propensity scores (a statistical matching technique that may account for possible covariates explaining the association) were accounted for. In contrast, Horwood et al. (2012) found that although there was a decrease in the strength of the association between marijuana use and depression after adjustment for confounders, the association remained significant.

One method to address possible confounders explaining an association between two variables is the twin study (Rutter, 2015). Twin studies take advantage of the inherent difference between monozygotic (MZ) and dizygotic (DZ) twins. MZ twins share 100% of their segregating genes, whereas DZ twins share, on average, 50% of their segregating genes. MZ and DZ twins share, by definition, all of the shared environmental influences (environmental influences that make sibling pairs more similar) as well. In MZ twins, any difference between them is due to non-shared environmental influences (environmental influences that lead to differences) in the twins. If the MZ twin who used more marijuana during adolescence were more depressed later in adulthood, the result would be consistent with a causal effect. However, this would not prove causality, because there may be non-shared environmental influences leading to both marijuana use and later depression (e.g., negative life events that influence one twin and not the other). In

contrast, an association between two variables may be due to common genetic or shared environmental influences.

Recently, Irons, Iacono and McGue (2014) conducted a longitudinal twin study that examined the association between early adolescent alcohol use and later outcomes. They found that use of the propensity score method to adjust for known confounding variables reduced the magnitude of the association, but that the twin method reduced the association further. They concluded that use of statistical tests to control for known or measured confounders may not be sufficient, and that the twin method may address unknown or unmeasured confounders.

Several studies have investigated the role of common genetic influences in marijuana abuse or dependence and depression. For instance, a twin study by Tsuang, Bar, Harley and Lyons (2001) found that the MZ twin who had depression also had greater prevalence of cannabis abuse or dependence, even after controlling for several confounders (education level, income and Vietnam combat experience). In contrast, several other genetically informative studies found evidence more consistent with common genetic or environmental influences. Fu et al. (2002) reported that the common genetic risk between depression and marijuana dependence is associated with antisocial personality disorder in men. Further, Marmorstein, Iacono, and McGue (2012) reported evidence suggesting that common genes explain the association between marijuana use and Major Depressive Disorder in an adoption design (which also has the ability to distinguish between genetic and environmental influences). Similarly, Lynskey et al. (2004) found that the comorbidity between marijuana dependence and Major Depressive Disorder (MDD) is most likely due to common genetic and environmental susceptibilities.

The present study examined the associations between childhood internalizing behavior, adolescent marijuana use and early adulthood depression. The first hypothesis is that the

correlation between marijuana use and depression is due to common genes or shared environmental influences. The second hypothesis is that after controlling for genetics and environmental factors on early internalizing behavior, the non-shared environmental factors that lead to marijuana use also lead to depression in adulthood; that is, the twin that used more marijuana is more depressed in adulthood. Results supporting the second hypothesis would be evidence consistent with a causal effect. These hypotheses are not mutually exclusive, and it is possible that both are true.

We also examined the possibility that childhood depressive symptoms occurring before marijuana exposure may influence adolescent marijuana use. In the present study, we were able to examine internalizing behavior assessed before the first occurrence of marijuana use, as these data were collected during the participants' childhood. Internalizing behavior during childhood has been identified as a possible predictor of later depression (Reinherz, Paradis, Giaconia, Stashwick & Fitzmaurice, 2003).

Methods

Participants

The participants were from Colorado's Longitudinal Twin Study (LTS), which consists of same-sex twin pairs born between 1986-1990, and recruited through the Colorado Department of Health. The LTS is 86.6% Caucasian, 8.5% Hispanic, 1.2% Asian, .7% African American and 2.9% other. The participants who were included in the present study were those who had at least one assessment of internalizing behavior, marijuana use or Major Depressive Disorder (MDD). The present study included 938 individuals, or 469 twin pairs. There were 132 MZ female pairs, 121 MZ male pairs, 104 DZ female pairs, and 112 DZ male pairs.

Measures

Internalizing Behavior

Only internalizing behavior known to be assessed before exposure to marijuana use was examined. Marijuana use was first assessed by the LTS researchers at age 12, and most participants had not yet initiated marijuana use. For the 10 participants who reported having initiated marijuana use by age 12, only internalizing behavior assessed before the age of onset reported by the participant was examined.

Internalizing behavior was reported by parents, teachers and children. The parent responses were assessed using the Child Behavior Checklist (CBCL; Achenbach 1991a) at ages 4, 5, 7, 9, 10 and 11. The teacher responses were assessed using the Teacher's Report Form (TRF; Achenbach 1991b), which is similar to the CBCL. The responses were taken at ages 7, 8, 9, 10 and 11. The responses from the children themselves were assessed using the Kandel Depressive Mood Inventory (KDMI; Kandel & Davies, 1982), a self-report questionnaire that assesses symptoms of depression. The responses were assessed at ages 9, 10, and 11.

The correlations for internalizing behavior assessed across the informants and across time points were generally positive and statistically significant. Results of confirmatory factor analyses suggested that a model with a higher order internalizing behavior factor with significant loadings on parent, teacher, and self-reported internalizing behavior factors (which had significant loadings on internalizing behavior assessed at each time point) fit the data well, $\chi^2(72)=127.42, p<.01; CFI=.97; TLI=.96; RMSEA=.03$. Because there was evidence for a latent internalizing factor, a composite variable (i.e., the average across all informants and time points) was used in subsequent analyses.

Marijuana Use

LTS researchers assessed the frequency of marijuana use when the participants were 17 years old via the Composite International Diagnostic Interview-Substance Abuse Module (CIDI-SAM). Participants indicated whether they did not use, used less than once per month, or used at least once per month.

Major Depressive Disorder (MDD)

LTS researchers used The Diagnostic Interview Schedule – IV (DIS-IV; Robins et al., 2000) to assess MDD at age 22. The DIS is a computerized interview designed to assess symptoms and diagnoses of major psychiatric disorders, according to the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2000). A categorical variable with three categories was examined: 0 indicating no symptoms, 1 indicating the presence of one or more symptoms but no diagnosis, and 2 indicating a diagnosis of MDD.

Analyses

All analyses were conducted using Mplus version 7 (Muthén and Muthén, 1998–2004),

which allows analyses of a combination of continuous and ordinal variables. Phenotypic, within-trait cross-twin, and cross-trait cross-twin correlations were calculated, then a Cholesky Decomposition, a type of multivariate analysis, was conducted.

The correlations between MZ and DZ twins were examined, and the magnitude of the genetic influences (A), shared environmental influences (C), and non-shared environmental influences (E) were estimated for each variable and the covariance between variables. Shared environmental influences are the environmental factors that lead to similarity between siblings. Non-shared environmental influences are environmental factors that lead to differences between siblings. As discussed, any difference between MZ twins can only be due to non-shared environmental influences. When examining the association between two different variables, MZ and DZ correlations are interpreted as follows: if the correlation for MZ twins is greater than the correlation for DZ twins, the results are consistent with common genetic influences. If the correlation for DZ twins is greater than half of the correlation for MZ twins, the results are consistent with common shared environmental influences. Lastly, if the correlation for MZ twins is less than the phenotypic correlation, the results are consistent with common non-shared environmental influences. The difference in MZ twins cannot be due to genetic or shared environmental influences; therefore any difference in marijuana use that is correlated with difference in MDD (between MZ twins) cannot be due to common genes or common shared environmental influences. In other words, if the MZ twin that used more marijuana during adolescence were more depressed later in adulthood, the result would be consistent with a causal effect.

Figure 1 illustrates the Cholesky Decomposition. This figure includes only the genetic influences and the non-shared environmental influences for simplicity. A1 and the corresponding

a11, a21, and a31 paths refer to genetic influences that affect all three variables. A2 and the corresponding a22 and a32 paths refer to genetic influences on adolescent marijuana use and early adulthood depression, after controlling for internalizing behavior. A3 and the corresponding a33 path refer to genetic influences that affect only early adulthood depression. E1, E2 and E3 follow this same pattern, but represent common non-shared environmental influences. Although not shown, the shared environmental influences (C1, C2, and C3) follow the same pattern as well.

If the a11, a21 and a31 paths are significant, it would demonstrate common genetic influences on all three variables, which would support the hypothesis that adolescent marijuana use and early adulthood depression are associated due to common genetic influences that also influence childhood internalizing behavior. If the e22 and e32 paths are significant, it would demonstrate common non-shared environmental influences between age 17 marijuana use and age 22 depression after statistically controlling for early childhood internalizing problems, supporting the hypothesis that adolescent marijuana has a causal influence on early adulthood depression.

Results

Descriptive Statistics

There were 574 participants with no depression symptoms, 90 with one or more depression symptoms but no diagnosis, and 99 with a diagnosis of MDD. For marijuana use, there were 469 participants who did not use, 131 who used less than once per month and 116 who used once per month or more.

Phenotypic and Cross Trait/Cross Twin Correlations

Table 1 shows the phenotypic, within-trait cross-twin, and cross-trait cross-twin correlations. A model in which correlations for males and females were free to vary, $\chi^2(42)=56.97$, $p=.06$; CFI=.98; TLI=.97; RMSEA=.06, and a model in which male and female correlations were constrained to be equal, $\chi^2(58)=67.99$, $p=.17$; CFI=.99; TLI=.98; RMSEA=.04, were tested. Both models fit the data well, and there was no significant difference in the fit of these two models, $\chi^2(16)=13.88$, $p=.61$. Therefore we interpreted the correlations from the model in which correlations are fixed to be equal across the two genders.

The phenotypic (within twin) correlations show that childhood internalizing behavior and MDD are positively correlated ($r=.21$, $p<.01$), and MDD and marijuana use are positively correlated ($r=.32$, $p<.01$). In addition, internalizing behavior and marijuana use are positively correlated at a trend level ($r=.09$, $p<.10$). The correlations suggest that there is evidence for genetic influences on internalizing behavior, marijuana use, and MDD, given correlations higher in MZ than DZ twins. There is also evidence for genetic influence on the covariance between internalizing behavior and marijuana use, as well as the covariance between marijuana use and MDD, given higher MZ than DZ correlations. Further, there is evidence for shared environmental influence on internalizing behavior, marijuana use, and MDD, as well as the

covariance between internalizing behavior and MDD and the covariance between marijuana use and MDD, given that the correlation for DZ twins is greater than half of the correlation for MZ twins. If marijuana use had a causal influence on MDD, we would find common non-shared environmental influences between these variables, as indicated by a phenotypic correlation that is higher than the MZ cross-trait cross-twin correlation, but the pattern of correlations does not suggest this.

Cholesky Decomposition

Figure 2 shows the results of the Cholesky model. None of the paths explaining the covariance between marijuana use and depression were statistically significant, although the overall covariance was statistically significant. The parameters from the Cholesky model were used to calculate the expected covariance between marijuana use and depression. For example, the covariance between marijuana use and depression due to genetic influences shared in common with internalizing behavior is obtained by multiplying path a21 and path a31 from Figure 1, $.46 \times .18 = .08$, and the covariance between marijuana use and depression due to genetic influences after controlling for internalizing behavior is obtained by multiplying path a22 and a32 from Figure 1, $.15 \times .34 = .05$.

Table 2 presents the six sources of the covariance between adolescent marijuana use and early adulthood depression. The first three sources of the covariance between marijuana use and depression are the genetic, shared environmental, and non-shared environmental influences that are shared in common with internalizing behavior. The second three sources of covariance are the genetic, shared environmental, and non-shared environmental influences on the covariance between marijuana use and depression after controlling for internalizing. Overall, the covariance between marijuana use and depression was $.32$. Shared environmental influences independent of

those also influencing internalizing behavior accounted for 75.72% of the covariance. The covariance due to non-shared environmental influences after controlling for internalizing behavior, (i.e., evidence that would be consistent with causation) accounted for only 7.43% of the variance. Thus, these results are inconsistent with the causal hypothesis.

Discussion

Previous research provides evidence that there is an association between marijuana use and depression, but the reason for the association is unclear. Some researchers have suggested that the association may exist because marijuana use causes depression, but this has not been confirmed (e.g., Degenhardt, Hall, & Lynskey, 2003). A considerable problem faced in the literature is the possibility of underlying confounding variables (e.g., familial influences that may be shared in common by marijuana use and depression) that cannot be addressed with other statistical analyses. We investigated the association between adolescent marijuana use and early adulthood depression in a prospective, longitudinal, genetically informative study. Specifically, the twin method, which can address unknown confounders, including common genetic and shared environmental influences, was used. In addition, given the longitudinal design, it was possible to address the potential influences on adolescent marijuana use and adulthood depression that are shared in common with depressive symptoms occurring before the first incidence of marijuana use (i.e., childhood internalizing behavior); this also allowed us to control for depression that occurred before marijuana use, as childhood internalizing behavior is correlated with later depression.

Our results indicated that there is a significant, positive correlation between adolescent marijuana use and early adulthood depression; this is consistent with findings in the literature. There were two hypotheses regarding the reason for this association: 1), the association is due to common genes or shared environmental influences, and 2), after controlling for genetics and environmental factors on early internalizing behavior, the non-shared environmental factors mediate the association (consistent with causality). Overall, the results suggested evidence consistent with hypothesis 1 rather than hypothesis 2.

The DZ cross-trait correlation for marijuana use and depression was more than half of the MZ correlation, indicating common shared environmental influences. Additionally, the Cholesky Decomposition results indicated that common shared environmental influences contributed most to the overall covariance between marijuana use and depression. If the results were consistent with the causal hypothesis, we would have found more evidence for non-shared environmental influence on the covariance between marijuana use and depression. MZ twins share all of their genetic material, and by definition, all of their shared environment. Therefore if the MZ twin who used more marijuana in adolescence is also more depressed in adulthood, this result is consistent with common non-shared environmental influences. It is important to note that, had we found evidence for common non-shared environmental influence, results would have been consistent with causality but not definitive evidence of causality as there may be common non-shared environmental influences (e.g. a negative life event that affects one twin and not the other) leading to both marijuana use and depression.

To further understand the association between marijuana use and depression, it would be beneficial to investigate possible specific shared environmental influences that may lead to both marijuana use and depression. Much of the environment shared between siblings is due to their family environment. An example of a family influence is parental monitoring, which has been associated with both lower adolescent marijuana use (e.g., Lac, & Crano, 2012), as well as adolescent depression (e.g., Yap, Pilkington, Ryan & Jorm, 2013). Another example is socio-economic status; lower socio-economic status has been associated with both higher prevalence of marijuana use (Lemstra, Bennett, Neudorf, Kunst, & Ushasri, 2008) as well as depression (e.g., Lorant, Deliége, Eaton, Robert, Phillippot & Ansseau, 2002). Parental monitoring and socio-economic status are both good candidates for a specific common shared environmental influence.

The following limitations should be considered while interpreting the results of the present study. Given the relatively small sample size, there was limited power to distinguish the influences of genetic, shared environmental, and non-shared environmental influences on the covariance between marijuana use and depression; it is possible that with a larger sample, we would be able to distinguish between the influences more accurately. Also, the sample was ascertained from the general population, and the percentage of participants that used marijuana frequently, or had an MDD diagnosis was low. It is possible that given a larger sample with more people who have used marijuana and had depression, we may be able to distinguish between the sources of covariance more accurately. Additionally, internalizing behavior may not be the most accurate way to control for depression before the initiation of marijuana use; our results suggest that there is a modest correlation between internalizing behavior and depression. Finally, although depression was assessed at age 22 years, the interview included lifetime prevalence of depression. We plan to conduct additional analyses that examine past year depression, in order to make sure that the assessment of adult depression does not include depression occurring before the initiation of marijuana use.

In conclusion, we found an association between adolescent marijuana use and early adulthood depression in a prospective, longitudinal twin study. The results indicated that the causal hypothesis is not supported, but that the association is mostly explained by shared environmental influence. Given these results, future research investigating possible specific environmental influences on both marijuana use and depression may lead to a better understanding of the association between marijuana use and depression.

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Table 1

Phenotypic and Cross-Trait/Cross-Twin Correlations.

	Internalizing	Marijuana	MDD	Internalizing-	Internalizing-	Marijuana
	Use	Use		Marijuana	MDD	Use-
				Use		MDD
<u>Females</u>						
Phenotypic				.15*	.21**	.28**
Monozygotic	.74**	.91**	.31*	.26**	.14	.28*
Dizygotic	.31**	.68**	.28	.02	.09	.22 ⁺
<u>Males</u>						
Phenotypic				.02	.22**	.36**
Monozygotic	.61**	.81**	.37*	.12	.15	.39**
Dizygotic	.45**	.84**	.20	-.15	.25**	.21
<u>All</u>						
Phenotypic				.09 ⁺	.21**	.32**
Monozygotic	.67**	.87**	.34**	.21**	.15*	.33**
Dizygotic	.36**	.78**	.24 ⁺	-.05	.16*	.21*

Note. ⁺ $p < .10$, * $p < .05$, ** $p < .01$.

Table 2

Sources of Covariance Between Marijuana Use and Depression.

	Covariance	Percentage of Total Covariance
<u>Shared in Common with Internalizing Behavior</u>		
A	.08	26.51
C	-.07	-23.35
E	-.01	-2.34
<u>After Controlling for Internalizing Behavior</u>		
A	.05	16.02
C	.24	75.72
E	.02	7.43
<u>Total Covariance</u>	.32	

Note. A = genetic influences; C = shared environmental influences; E = non-shared environmental influences.

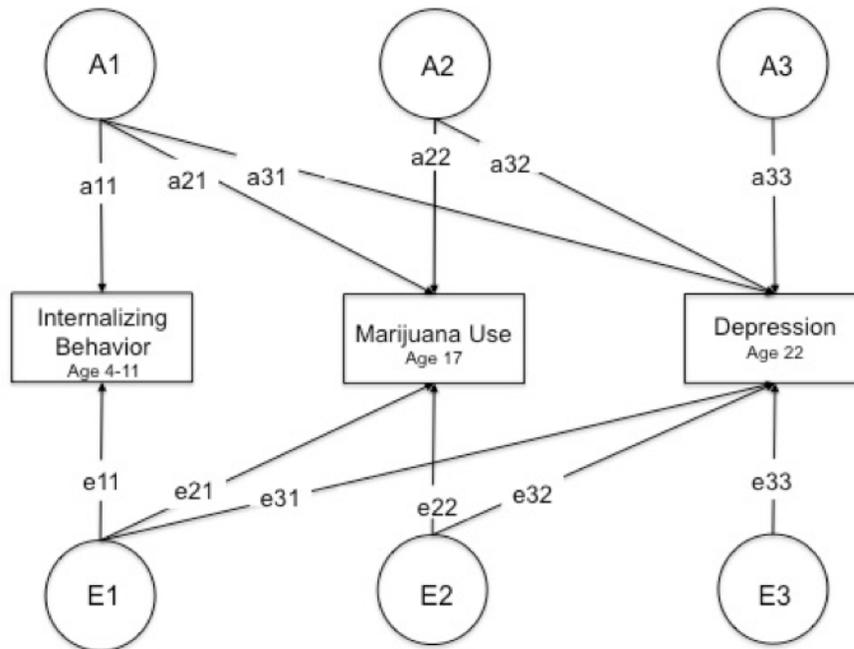


Figure 1. Cholesky Decomposition, showing only the genetic (A) and non-shared environmental (E) influences and their corresponding pathways. A1 = genetic influences on internalizing behavior, marijuana use and depression; A2 = genetic influences on marijuana use and depression after controlling for internalizing behavior; A3 = genetic influences specific to depression; E1 = common non-shared environmental influences on internalizing behavior, marijuana use and depression; E2 = non-shared environmental influence on marijuana use and depression after controlling for internalizing behavior; E3 = non-shared environmental influence specific to depression; a_{11} = A1's influence on internalizing behavior; a_{21} = A1's influence on marijuana use, a_{31} =A1's influence on depression; a_{22} =A2's influence on marijuana use; a_{32} =A2's influence on depression; a_{33} =A3's influence on depression; e_{11} =E1's influence on internalizing behavior; e_{21} =E1's influence on marijuana use; e_{31} =E1's influence on depression; e_{22} =E2's influence on marijuana use; e_{32} =E2's influence on depression; e_{33} =E3's influence on depression.

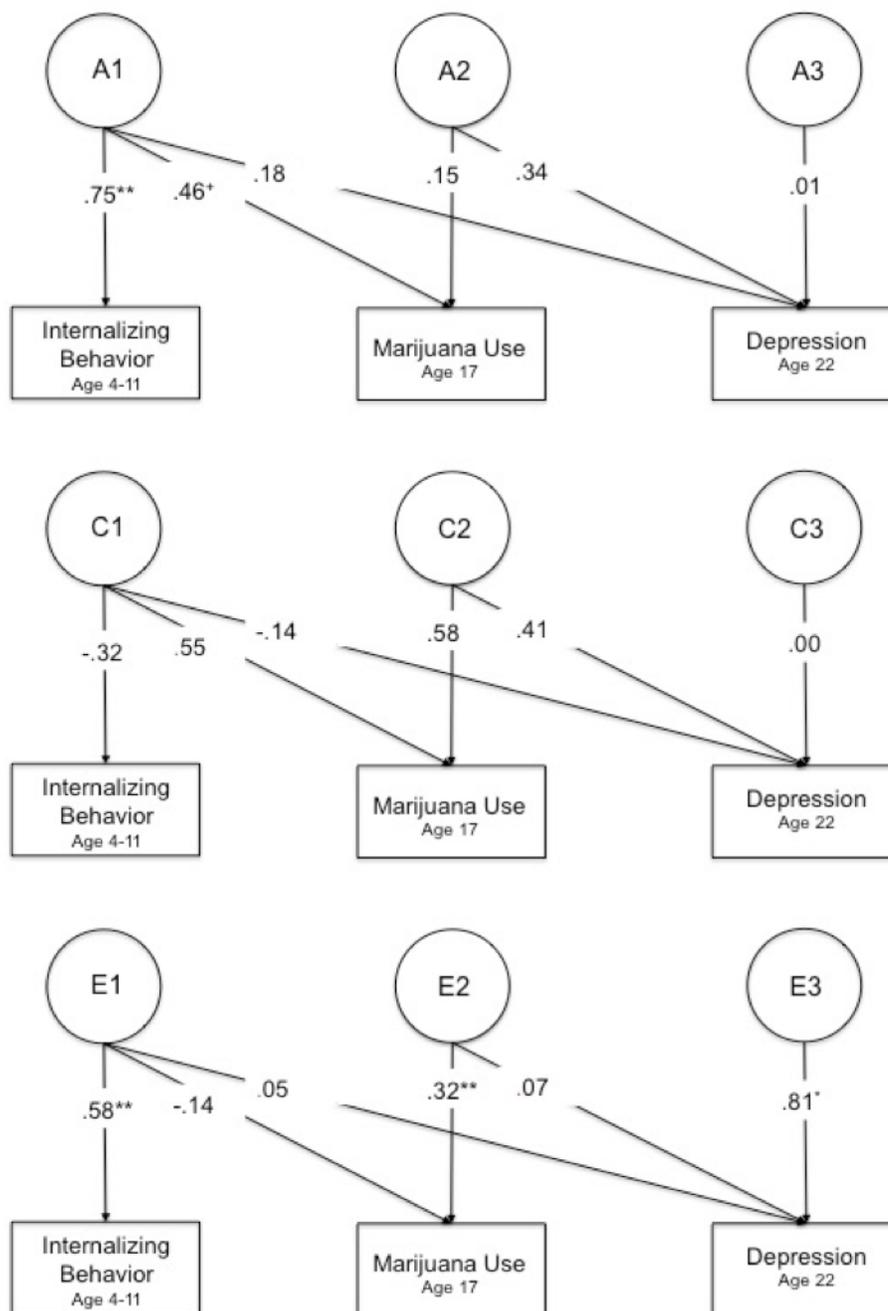


Figure 2. Results of the Cholesky Decomposition. A1 = genetic influences on internalizing behavior, marijuana use and depression; A2 = genetic influences on marijuana use and depression after controlling for internalizing behavior; A3 = genetic influences specific to depression; C1 = shared environmental influences on internalizing behavior, marijuana use and depression; C2 = shared environmental influences on marijuana use and depression after controlling for internalizing behavior; C3 = shared environmental influences specific to depression; E1 = common non-shared environmental influences on internalizing behavior, marijuana use and depression; E2 = non-shared environmental influences on marijuana use and depression after controlling for internalizing behavior; E3 = non-shared environmental influences specific to depression.

⁺ $p < .10$, * $p < .05$, ** $p < .01$.